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AU Guay David R P
CS Department of Experimental and Clinical Pharmacology, Institute for the
Study of Geriatric Pharmacotherapy, College of Pharmacy, University of
Minnesota, Minneapolis, Minnesota, USA. guayx001@umn.edu
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Oxcarbazepine, Topiramate, Zonisamide, and Levetiracetam: Potential Use in Neuropathic Pain

David R.P. Guay, PharmD

Department of Experimental and Clinical Pharmacology, and Institute for the Study of Geriatric Pharmacotherapy, College of Pharmacy, University of Minnesota, and PartneringCare Senior Services, Division of Geriatrics, HealthPartners, Minneapolis, Minnesota

ABSTRACT

Background: Oxcarbazepine, topiramate, zonisamide, and levetiracetam are the antiepileptic drugs (AEDs) most recently approved by the US Food and Drug Administration. Based on the experience with carbamazepine, gabapentin, and lamotrigine, these newer AEDs are being investigated for the management of neuropathic pain.

Objective: This article reviews preclinical and clinical data on the efficacy and tolerability of these 4 AEDs in the management of neuropathic pain, as well as the pharmacokinetics, drug-interaction potential, adverse effects, and dosing of these agents, with an emphasis on their use in older individuals.

Methods: Relevant studies were identified through a MEDLINE search of the English-language literature published between 1986 and May 2003, a review of the reference lists of identified articles, and abstracts from the annual meetings of the American Academy of Neurology (1986–2002) and the 2003 Annual Meeting of the American Pain Society. Search terms were *oxcarbazepine, topiramate, zonisamide, and levetiracetam*.

Results: Oxcarbazepine and topiramate have been effective in animal models of neuropathic pain. Thirty-four publications on the efficacy and tolerability of the 4 agents were identified (25 case reports/case series, 6 randomized parallel-group studies, and 3 randomized crossover studies). The 9 randomized studies were restricted to oxcarbazepine and topiramate, and 23 (68%) publications were available in abstract form only. These preliminary data suggest that the 4 newer AEDs may be useful in a wide variety of neuropathic pain syndromes; however, additional data, including full-length peer-reviewed reports, are necessary before their true analgesic potential in neuropathic pain can be determined. All 4

agents have pharmacodynamic interactions with other psychotherapeutic drugs, potentiating adverse central nervous system events such as sedation. With the exception of levetiracetam, these drugs also have pharmacokinetic interactions with other drugs, although to a somewhat lesser extent than carbamazepine. These agents have some unique adverse effects not frequently monitored by clinicians, such as hyponatremia, nephrolithiasis, acute myopia with secondary angle-closure glaucoma, and weight loss.

Conclusions: Based on preliminary data, oxcarbazepine, topiramate, zonisamide, and levetiracetam may be useful in the treatment of a wide variety of neuropathic pain syndromes, although full publication of the results of controlled trials is awaited. These agents are associated with specific adverse effects not commonly monitored by clinicians. Of the 4, levetiracetam appears to be easiest to use (ie, no need for dose adjustment in organ dysfunction, no need for laboratory monitoring) and best tolerated, and has not been associated with the unique toxicities seen with oxcarbazepine, topiramate, and zonisamide. The ultimate role of these agents in the therapeutic armamentarium against pain requires further research and experience. In the interim, these 4 agents should be used to treat neuropathic pain in the elderly only when carbamazepine, gabapentin, or lamotrigine cannot be used or when the response to the aforementioned agents is sub-optimal. (*Am J Geriatr Pharmacother.* 2003;1:18–37) Copyright © 2003 Excerpta Medica, Inc.

Key words: oxcarbazepine, topiramate, zonisamide, levetiracetam, neuropathic pain, antiepileptic drugs.

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INTRODUCTION

Antiepileptic drugs (AEDs) are among the adjunctive drugs of choice for neuropathic pain of various types.¹ The most commonly administered AED for pain has traditionally been carbamazepine. Newer AEDs, such as gabapentin and lamotrigine, may be even more useful and have been reviewed recently.^{2,3} The AEDs are generally better tolerated than the tricyclic antidepressants (TCAs). There is considerable intersubject and intrasubject variability in the pain-relief response to AEDs, making monitoring of serum drug concentrations of little practical value.⁴ The variability in response to carbamazepine, gabapentin, and lamotrigine has led to preliminary investigations of the most recently approved AEDs for the management of neuropathic pain.

This article reviews preclinical and clinical data on the efficacy and tolerability of oxcarbazepine, topiramate, zonisamide, and levetiracetam in the management of neuropathic pain, as well as the pharmacokinetics, drug-interaction potential, adverse effects (AEs), and dosing of these agents, with an emphasis on their use in older individuals. Relevant English-language publications were identified through a search of MEDLINE from 1986 through May 2003 using the search terms *oxcarbazepine*, *topiramate*, *zonisamide*, and *levetiracetam*. All articles dealing with these agents in the context of pain/analgesia were considered for review, as were their reference lists. Relevant abstracts from annual meetings of the American Academy of Neurology (1986–2002) and the 2003 Annual Meeting of the American Pain Society were also included.

NEUROPATHIC PAIN IN THE ELDERLY

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system.⁵ Pain arising from disorders of the central nervous system (CNS) or peripheral nervous system has traditionally been classified by anatomic site and underlying pathology (usually axonal degeneration, segmental demyelination, or both). Classification systems based on the presumed etiology, such as metabolic (diabetes, hypothyroidism, amyloidosis), compression (tumor), toxic (various drugs), and infectious (postherpetic), have also been used. Others have advocated a mechanistic approach (ie, stimulus-independent vs stimulus-evoked pain) to more precisely define the clinical features of specific syndromes.⁶

Many of the underlying causes of neuropathic pain are degenerative or age related. Thus, it is not surprising that neuropathic pain syndromes are more common in the

elderly. In the general geriatric population, the incidence of neuropathic pain is probably second only to that of musculoskeletal pain.⁷ The most common neuropathic pain syndromes in the elderly stem from strokes (central poststroke pain, thalamic pain), diabetes (painful diabetic neuropathy), herpes zoster infection (postherpetic neuralgia [PHN]), and trigeminal neuralgia.^{7,8} Other causes that are more common in elderly compared with younger individuals include nutritional deficiencies, hypothyroidism, multiple myeloma, use of nitrofurantoin (for long-term prophylaxis of urinary tract infection) or isoniazid, connective tissue disease, peripheral vascular disease, and nontraumatic lower limb amputation.⁹ Because surgery is a common mode of treatment for the maladies of advancing age, postoperative pain syndromes (eg, intercostal neuralgia after thoracotomy, ilioinguinal neuralgia after hernia repair, radicular spinal pain) are not uncommon in older individuals.¹⁰

Although the symptoms and signs of neuropathic pain are similar in older and younger individuals, certain factors that may be present in older individuals can make assessment and management of neuropathic pain more difficult. These include the presence of an affective (depressed mood) component, modified pathophysiology, cognitive impairment, altered pharmacology (pharmacokinetics and pharmacodynamics), poor adherence to therapeutic regimens, and difficulty in assessing the suitability of particular patients for nonpharmacologic interventions.¹¹

For these reasons, any drug being assessed for efficacy and tolerability in the management of neuropathic pain in the older population should undergo a core group of clinical trials. This core should include trials investigating the effects of aging and renal impairment on the drug's pharmacokinetics, and trials of potential drug-drug interactions with agents commonly used in older individuals that either have a narrow therapeutic margin or might potentially compromise efficacy by reducing drug bioavailability. Comparative trials including placebo and active comparators also need to be performed in the most common neuropathic pain syndromes in the elderly (at a minimum, painful diabetic neuropathy and PHN).

THE EXPERIENCE WITH GABAPENTIN

There is a large quantity of data regarding the efficacy and tolerability of gabapentin in the management of neuropathic pain. Open-label case reports and case series have involved >750 patients, and published controlled trials have included >500 patients with painful diabetic neuropathy, PHN, or multiple sclerosis. In human models of neuropathic pain, gabapentin has been effective

against both spontaneous and evoked pain. At dosages up to 3.6 g/d, gabapentin has been effective in a variety of neuropathic pain syndromes, including those refractory to TCAs and other AEDs. Despite the higher costs of gabapentin, many clinicians prefer this agent to TCAs and carbamazepine in the elderly.

Gabapentin is approved by the US Food and Drug Administration for the treatment of PHN in adults. At present, gabapentin is considered first-line therapy for neuropathic pain in the elderly. When dosed appropriately, it is well tolerated in the older population, even in the presence of renal impairment. CNS toxicity, including somnolence, dizziness, ataxia, tremor, and diplopia, is the major AE concern with this drug. A lack of clinically important drug-drug interactions makes gabapentin easier and safer to use in an elderly population receiving multiple drug therapies. Saturable absorption from the gastrointestinal tract and a short terminal disposition half-life ($t_{1/2}$) in the presence of normal renal function necessitate multiple (3–4) daily doses, with an attendant risk of nonadherence.^{3,12–15} Further data are needed, however, in the frail elderly in long-term care facilities.

MECHANISMS OF ACTION OF OXCARBAZEPINE, TOPIRAMATE, ZONISAMIDE, AND LEVETIRACETAM

Although the mechanisms of analgesic activity of oxcarbazepine, topiramate, zonisamide, and levetiracetam are not known, it has been suggested that they relate to these agents' anticonvulsant activity. With the exception of levetiracetam, these newer AEDs have mechanisms of anticonvulsant activity similar to those of the older agents. Oxcarbazepine and its active 10-hydroxy metabolite inhibit voltage-dependent sodium channels, and the metabolite also inhibits potassium channels.¹⁶ Topiramate inhibits voltage-dependent sodium channels, potentiates inhibitory gamma-aminobutyric acid (GABA)-ergic neurotransmission, antagonizes the kainate or alpha-amino-3-hydroxy-5-methyl-4-isoxazole subtype of the glutamate receptor, and inhibits carbonic anhydrase.¹⁷ Zonisamide inhibits voltage-dependent sodium and T-type calcium channels and carbonic anhydrase.¹⁸ Levetiracetam inhibits calcium channels and delayed-rectifier potassium currents and antagonizes negative allosteric modulators of the GABA and glycine responses at a nonbenzodiazepine site.¹⁹

PRECLINICAL STUDIES IN ANALGESIA

Few data have been published from *in vitro* and animal studies of these 4 agents as analgesics. Ichikawa et al²⁰ and

Kiguchi et al²¹ examined the effects of oxcarbazepine and its 10-hydroxy metabolite in 2 well-established animal models of neuropathic pain: superficial peroneal nerve single-fiber excitation and tooth pulp-evoked potentials in the trigeminal spinal tract nucleus, both in anesthetized cats. Both moieties acted as dose-dependent inhibitors of evoked potentials in these models, supporting further evaluation of oxcarbazepine as an analgesic compound. Topiramate has been evaluated in the Chung model of neuropathic pain (allodynia and hyperalgesia in the hind paws of rats subjected to tight ligation of the lumbar spinal nerves).²² It acted as a dose-dependent inhibitor of allodynia in both single- and repeated-dose studies, supporting further evaluation of this compound as an analgesic.

CLINICAL STUDIES IN ANALGESIA

Thirty-four publications on the efficacy and tolerability of the 4 agents were identified, the majority of them case reports or case series (25 case reports/case series, 6 randomized parallel-group studies, and 3 randomized crossover studies). The 9 randomized studies were restricted to oxcarbazepine and topiramate, and 23 (68%) publications were available in abstract form only. These reports are summarized in tables appearing in the following sections. Although the results suggest efficacy, case reports and case series do not constitute definitive proof. Only randomized, placebo- or active-controlled trials can do this, particularly given the substantial placebo response rates in chronic pain studies. In addition, noncontrolled reports tend to overstate efficacy and understate toxicity.

An important potential confounder in pain studies is the continuation of baseline analgesia during use of the compound of interest. Many noncontrolled reports do not discuss whether baseline analgesia was or was not discontinued or tapered off during the initiation of study therapy. This may also be a concern in controlled trials in which drug/placebo or drug/active comparator are added to baseline therapy. In cases in which baseline analgesia is continued, it is impossible to distinguish the analgesic effect of the compound of interest from that of the combination of agents because of possible antagonistic, additive, or synergistic pharmacodynamic effects or pharmacokinetic drug-drug interactions.

OXCARBAZEPINE

Table I summarizes the results of case reports, case series, and controlled clinical trials of oxcarbazepine in neuropathic pain.^{23–38} The pharmacokinetic parameters of oxcarbazepine are summarized in Table II.^{16–19,39–42}

Table I. Efficacy data for oxcarbazepine (OXCARB) in the management of neuropathic pain.

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
23	Refractory cutaneous allodynia	CR	3 (2 M, 1 F)	50 (M), 55 (F), 77 (M)	150 mg BID initially, titrated to pain relief or MTD. Maximum dose, 600–1200 mg/d. Duration of therapy NR.	VAS scores decreased ≥50% from baseline in all patients. One patient discontinued all opioid use and another reduced oxycodone use from 6 U/d to 2 U/wk.
24	Notalgia parasthetica	CR	2 (F)	29	300 mg BID for 6 mo.	Pain score decreased from 6/10* at the end of 1 mo to 3/10 at the end of 6 mo.
				NR	300 mg BID for 2 wk, with increase to 600 mg BID for 5.5 mo.	Pain score decreased from 8/10 at the end of 1 mo to 3/10 at the end of 6 mo.
25	Trigeminal neuralgia	CR	1 (M)	40	300 mg BID for 4 mo.	Pain was reported to remit shortly after initiation of therapy and did not recur during therapy. Therapy discontinued after 4 mo without "immediate" recurrence of pain. Since then, pain has recurred yearly, "always easily controlled" by initiation of OXCARB therapy.
26	Trigeminal neuralgia†	CS	6 (4 F, 2 M)	Mean, 61 (range, 42–77)	Titration schedule NR. Optimal daily doses (dose at which patient was pain free for 2 wk), 1200–2400 mg (1200 mg/d in 2 patients, 1500 mg/d in 1, 2100 mg/d in 2, 2400 mg/d in 1). Doses given BID–QID.	Onset of effect within 24 hours in all patients. Pain alleviation reported to be excellent in all patients. Therapeutic range of 10-hydroxy metabolite for analgesia 50–100 µmol/L. Mild hyponatremia (serum Na, 123–131 mmol/L) occurred in 2 patients.
27	Refractory trigeminal neuralgia†	CS	15 (11 F, 4 M)	Mean, 55 (range, 38–78)	In first 5 patients, all previous therapy was discontinued for 1 wk before gradual introduction of OXCARB; in remaining 10 patients, OXCARB was introduced gradually while previous therapy was slowly withdrawn. Each 200 mg CBZ or 100 mg PHT was replaced by OXCARB 300 mg q3d until the switchover was complete. OXCARB was dosed QID. Mean follow-up, 16 y (range, 8–30 y). Mean duration of treatment, 4.0 y (range, 2.4 mo–10.8 y). Mean daily dose, 1200 mg. Maximum daily dose, 600–3000 mg; minimum daily dose, 300–1800 mg.	In 7 patients, intermittent PHT (100–300 mg/d) was added to help control symptoms. In 5 patients, TCAs were used continuously for dull aching background pain. Eight patients used OXCARB continuously, and 7 discontinued OXCARB when pain went into remission for periods of 2–7 mo (with the exception of 1 patient who discontinued OXCARB for 26 mo). Efficacy, initially noted in all patients, was short-lived, and 12 patients eventually required surgery. The most common AEs were tiredness (6); sedation/dizziness (5 each); poor concentration, ataxia, diplopia, and ankle edema (3 each); and nausea, constipation, and headache (1 each). Significant (not defined) dose-dependent hyponatremia reported (mean serum Na decreased from 139 to 131 mmol/L at maximum doses). Mean time from initiation of OXCARB to surgery or death, 5.6 years. Mean time to recurrence of pain with OXCARB and surgery over first 3 y, 10 and 28 mo, respectively ($P < 0.001$).

(continued)

Table I. (Continued)

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
28	Trigeminal neuralgia [§]	CS	13 (7 F; 6 M)	Mean, 69 (range, 59–85)	Initial daily dose, 400–1200 mg (mean, 850 mg); maximum daily dose, 400–2000 mg (mean, 1100 mg). Titration schedule NR. Doses given BID–TID. Duration of treatment, 1–36 mo (mean, 10 mo).	Nine (69%) patients were pain free; 3 (23%) had “decided remission,” with less frequent or less intense paroxysms of pain that occurred only on excitation of the “trigger zone”; 1 (8%) had no response. Onset of effect within 24 h in 6 patients, 48 h in 4, 72 h in 3, and on day 7 in 1 (N = 14, as reported). Dose reductions of 25% to 50% self- initiated by 5 patients led to pain recurrence within 1–2 d. Five (83%) of 6 patients who had previously received CBZ judged the effect of OXCARB superior to that of CBZ; 1 (17%) reported the reverse. One (8%) of 12 patients who responded initially had a recurrence after 6 mo despite continuous therapy.
29	Refractory trigeminal neuralgia	CS	56 (34 F; 22 M)	59	Duration of treatment 0.5–11 y. Switch from controlled-release CBZ to OXCARB monotherapy (dosage regimen NR). OXCARB doses generally 1–3 times those of CBZ.	Pain “well controlled” in 43 (77%) patients receiving OXCARB monotherapy; 13 (23%) patients had incomplete relief or prematurely discontinued therapy due to AEs. Eleven of the 43 (26%) patients whose pain was controlled elected surgical treatment after a mean 5 y of OXCARB therapy. Hyponatremia was mentioned, but data NR.
30	CBZ- responsive trigeminal neuralgia with AEs to CBZ	CS	50 (NR)	NR	Patients considered for reduction in CBZ dose and combination OXCARB + CBZ therapy or switch from CBZ to OXCARB. Regimens and duration of therapy NR.	26 (52%) patients received combination therapy. 24 (48%) received OXCARB monotherapy. In 22 (92%) of the 24 patients receiving OXCARB monotherapy, efficacy was comparable to that of previous CBZ therapy.
31	Refractory postherpetic neuralgia	CS	12 (NR)	NR	150 mg BID, with increase to 600 mg BID (titration schedule NR). Duration of study, 12 wk.	Mean (SD) pain score at its worst, 9.7 (0.8) at baseline, 5.5 (0.9) at wk 4, 5.2 (0.9) at wk 8, 4.8 (0.6) at wk 12. Mood score, 8.3 (1.2), 4.6 (1.2), 4.5 (1.2), 3.7 (0.6), respectively. ADL score, 8.3 (1.0), 5.0 (1.4), 4.5 (0.9), 3.9 (0.3). Sleep score, 8.3 (1.1), 4.1 (0.9), 3.6 (0.6), 3.3 (0.6). Patient's global assessment, 272 (9), 63.3 (11.4), 66.3 (9.2), 69.1 (10.4). Statistical analysis NR.

(continued)

Table I. (Continued)

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
32	Various painful peripheral neuropathies	CS	10 (NR)	Mean, 47 (range, 24-66)	300 mg/d initially, titrated every 2-5 d to a maximum of 1500 mg/d, efficacy, or MTD. Effective doses ranged from 900-1200 mg/d. Duration of therapy NR.	Mean baseline VAS pain score (10-cm scale), 8.7 cm; mean VAS score at wk 8, 3.4 cm. Seven (70%) patients had a response (defined as $\geq 50\%$ decrease from baseline VAS score). Response evident from wk 2 and stable from wk 4 onward. Response poorer with more severe axonal involvement of peripheral nerves. AEs included transient somnolence and dizziness (data NR).
33	Various refractory neuropathic pain syndromes	CS	7 (NR)	NR	150 mg BID initially, with titration to pain relief or MTD. Maximum dose, 150-1200 mg/d given in divided doses. Duration of therapy NR.	Baseline VAS pain score (100-mm scale), 32-80 mm. At final on-therapy evaluation, VAS score had decreased in all patients (range, 8-43 mm). Relief sustained for ≥ 1 y in 6 (86%) patients and for 6 mo in 1 (14%). Three (43%) patients discontinued all concomitant analgesics, 1 (14%) discontinued all opioids, and 2 (29%) reduced daily gabapentin dose. No clinically significant AEs reported.
34	Refractory postherpetic neuralgia	CS	24 (12 M, 12 F)	Mean, 71	150 mg/d initially, titrated every 2 d to 900 mg/d. Duration of treatment, 8 wk.	Nineteen (79%) patients completed treatment; 3 (13%) discontinued treatment due to lack of efficacy during titration and 2 (8%) due to AEs (dizziness, nausea, sedation). Efficacy evident during wk 1. Allodynia disappeared almost completely in all patients. Patient's global assessment very good in 50%, good in 29%, and not applicable in 21% (discontinued early). No AEs in the 19 patients who completed the study.
35	Trigeminal neuralgia [†]	R, DB, CO	15 (NR)	NR	Titration to MTD of CBZ (400-1200 mg/d) and OXCARB (900-2100 mg/d), each for 3 wk. No data on washout between treatments.	Twelve (80%) patients reported similar analgesia with the 2 agents; 2 (13%) reported significantly better analgesia with OXCARB, and 1 (7%) reported significantly better analgesia with CBZ.

(continued)

Table I. (Continued)

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
36	New-onset trigeminal neuralgia	R, DB, PG	46 (NR)	≥40	Randomization to OXCARB 300 mg BID or CBZ 200 mg BID, titrated over 2–4 wk to most effective dose for 4-wk maintenance period. Most frequent maintenance doses, OXCARB 750 mg/d and CBZ 500 mg/d.	Differences in efficacy variables for spontaneous and evoked pain NS between OXCARB (n = 24) and CBZ (n = 22). 100% responded and 50% became pain free in both groups. Significant reductions in evoked pain in 70% of OXCARB recipients and 59% of CBZ recipients (statistical analysis NR). Global assessment of efficacy good or excellent in 96% of OXCARB recipients and 91% of CBZ recipients. Global assessment of tolerability good or excellent in 68% of OXCARB recipients and 52% of CBZ recipients. ¹ OXCARB recipient discontinued prematurely due to rash.
37	Trigeminal neuralgia	R, DB, PG	130 (NR)	≥40	Pooled analysis of 3 studies of identical design. Randomization to OXCARB or CBZ, titrated over 2–4 wk to most effective dose for 4-wk maintenance period. Median daily doses, OXCARB 750 mg and CBZ 500 mg in patients with new-onset disease; 1050–1200 mg and 700–900 mg, respectively, in treatment-refractory disease.	Results not presented separately for those with new-onset and refractory disease. Differences in efficacy variables for spontaneous and evoked pain NS between OXCARB (n = 69) and CBZ (n = 61). Reduction in number of weekly attacks, 91% and 88%, respectively; reduction in evoked pain, 58% and 62%. Global assessment of efficacy good or excellent, 78% and 81%; global assessment of tolerability excellent, 53% and 38% (statistical analysis of tolerability NR). AE data NR.
38	Cancer-related neuropathic pain	R, PG	20 (12 F, 8 M)	Range, 28–85	Randomization to OXCARB (n = 10) or AMI (n = 10), with opioids gradually discontinued (decreased by 10% qod or as tolerated). Regimens NR.	After 6 mo, pain control was comparable between groups. AEs occurred less frequently in OXCARB group. No withdrawal symptoms in OXCARB group, and withdrawal of opioids easier in this group. Quantitative data NR.

CR = case report; M = male; F = female; MTD = maximum tolerated dose; NR = not reported; VAS = visual analog scale; CS = case series; CBZ = carbamazepine; PhT = phenytoin; TCAs = tricyclic antidepressants; AEs = adverse effects; ADL = activities of daily living; R = randomized; DB = double-blind; CO = crossover; PG = parallel-group; AMI = amitriptyline.

^{*}Scale from 0/10 = no pain to 10/10 = worst imaginable pain.

[†]Pain refractory to CBZ (n = 4) or patient allergic to CBZ (n = 2).

[‡]Complete pain relief not achieved with CBZ.

[§]Six patients had received CBZ previously.

^{||}Scale from 0 = no pain, best mood, most ADL, best sleep, to 10 = worst pain, worst mood, least ADL, worst sleep.

[¶]Scale from 0 = poor to 100 = most satisfied.

Table II. Pharmacokinetic parameters for oxcarbazepine, topiramate, zonisamide, and levetiracetam.^{16-19,39-42}

Drug	F, %	T _{max} , h	PPB, %	Vd/F, L/kg	t _{1/2} , h	CL/F, mL/min
Oxcarbazepine*	—	4–6	37–43	0.7–0.8	9	0.85 [†]
Topiramate	81–95	1–4	9–17	0.6–0.8	20–30 [‡] 8–15 [§]	20–30 [‡] 40–60 [§]
Zonisamide	≥50	2–5	40–50	1.5	56 [¶] 63–69 ^{‡¶} 105 [¶] 25–35 [§]	17–24 [‡] 30–50 [§]
Levetiracetam	>95	1	<10	0.5–0.7	6–8 [‡] 5–8 [§]	0.96 [†]

F = oral bioavailability; T_{max} = time to maximum plasma concentration; PPB = plasma protein binding; Vd/F = apparent volume of distribution; t_{1/2} = terminal disposition half-life; CL/F = apparent total body clearance.

*Data refer to the active 10-hydroxy metabolite.

[†]mL/min per kg.

[‡]Healthy volunteers.

[§]Recipients of enzyme-inducing antiepileptic drugs.

[¶]Single dose.

^{||}Multiple dose to steady state.

[¶]In red blood cells.

Pharmacokinetics

Oxcarbazepine is a keto analogue of carbamazepine having the chemical formula 10,11-dihydro-10-oxo-carbamazepine. Oxcarbazepine may be considered a prodrug for the active 10-hydroxy metabolite (10,11-dihydro-10-hydroxy-5H-dibenzo(b,f)azepine-5-carboxamide, or MHD). After essentially 100% absorption, oxcarbazepine is converted to MHD almost immediately by reduction of the keto group by cytosol arylketone reductase. Food exerts no clinically significant effect on the absorption of oxcarbazepine. The pharmacokinetics of MHD are linear (ie, maximum plasma concentrations [C_{max}] and area under the plasma concentration–time curve [AUC] increase in proportion to increasing dose).⁴³ Plasma protein binding of oxcarbazepine and MHD are not altered in patients with trigeminal neuralgia.⁴⁴ MHD is glucuronidated or converted to the dihydroxy or transdiol derivative (10,11-dihydro-10,11-trans-hydroxycarbamazepine, or DHD), a reaction catalyzed by the cytochrome P450 (CYP) system. In contrast to carbamazepine, neither oxcarbazepine nor MHD undergoes autoinduction (ie, stimulates its own metabolism). Ninety-six percent of the oxcarbazepine dose is excreted in urine (83% as MHD or MHD glucuronide, ≤3% as oxcarbazepine, 4%–7% as DHD).

Based on single- and multiple-dose studies,⁴³ the C_{max} and AUC of MHD are 30% to 60% higher in elderly vol-

unteers (age 60–82 years) compared with young volunteers (age 18–32 years). This difference can be accounted for by age-related reductions in creatinine clearance (CrCl). There is a linear correlation between CrCl and renal clearance of MHD: when CrCl is <30 mL/min, the mean t_{1/2} of MHD is prolonged to 19 hours and the mean AUC is increased 2-fold. Mild to moderate hepatic impairment (Child-Pugh classes A and B) does not significantly alter the pharmacokinetics of oxcarbazepine or MHD. Data are not available regarding the effect of severe hepatic impairment (Child-Pugh class C).⁴³

Drug Interactions

In contrast to carbamazepine, oxcarbazepine and MHD are not generalized inducers of hepatic enzymes. They selectively induce the CYP3A4/3A5 isozyme, enhancing the metabolism of estrogen (mean decrease in AUC, 48%), progestogen (mean decrease in AUC, 32%), and felodipine (mean decrease in C_{max}, 34%; mean decrease in AUC, 28%). Induction of uridine diphosphate (UDP)-glucuronyl transferase activity occurs, leading to enhanced glucuronidation and elimination of lamotrigine (eg, mean decrease in C_{max}, 29%). Inhibition of the CYP2C19 isozyme by oxcarbazepine/MHD can produce increases in phenytoin and phenobarbital concentrations of up to 40% and 14%, respectively. Hepatic enzyme inducers such as carbamazepine, phenobarbital, and phenytoin enhance apparent

total body clearance (CL/F) of MHD by 25% to 40%. Verapamil and valproate may also reduce plasma concentrations of MHD by unknown mechanisms.⁴⁰

Adverse Effects

Based on the results of double-blind trials in patients with epilepsy,^{16,41,45,46} the most common AEs with oxcarbazepine include sedation, headache, dizziness, rash, vertigo, ataxia, nausea, and diplopia. These effects appear to be dose dependent, occurring at higher frequencies as the dose increases. Behavioral effects such as depression and mania occur rarely.⁴⁷ Rash occurs less frequently with oxcarbazepine than with carbamazepine, and the rate of cross-reactivity is ~30%.⁴⁶ Unlike carbamazepine, oxcarbazepine has been associated with no hepatic or hematologic toxicities. Although hyponatremia is thought to occur more frequently with oxcarbazepine than with carbamazepine, at least some of this difference may be accounted for by the enhanced monitoring mandated in oxcarbazepine study protocols. The frequency of hyponatremia with oxcarbazepine has been reported to range from 22% to 73%.⁴⁶ Most cases are asymptomatic, but severe cases are occasionally seen. Most cases arise in the first 3 months of therapy, and risk factors include older age, premenopausal female, greatly increased fluid intake (eg, psychogenic polydipsia), renal impairment, postoperative status, and concurrent use of other drugs that can also reduce serum sodium.

The mechanism of the latter effect is unclear but is presumed to be complex, including changes in osmoreceptor sensitivity, release of antidiuretic hormone (ADH), sensitivity of kidney ADH receptors, a direct effect on renal tubular cells, and/or suppression of ADH breakdown. Serum ADH can be normal, increased, or decreased. Frequent electrolyte monitoring is recommended, particularly during the first 3 months of therapy.⁴⁸

The safety and tolerability of oxcarbazepine have been compared in patients with epilepsy aged ≥ 65 years ($n = 52$) and aged 18 to 64 years ($n = 1574$).⁴⁸ Premature discontinuation rates due to AEs and AE profiles were similar in the 2 populations. The most common AEs in the older group were vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%), compared with headache (32%), dizziness (29%), somnolence (24%), and nausea (20%) in the younger group. Asymptomatic hyponatremia occurred in 3 older patients.

Dosing

Oxcarbazepine is available as oral tablets (150, 300, and 600 mg) and as an oral suspension (300 mg/5 mL).

Based on data from the trials in epilepsy,^{16,41,45,46} the recommended adult starting dosage is 300 to 600 mg/d, slowly titrated at weekly intervals, based on response, to a usual maintenance dosage of 600 to 1200 mg/d. The drug is given 2 or 3 times daily. In patients with a CrCl < 30 mL/min, the initial starting dose should be halved, followed by titration to response.

Carbamazepine can be replaced by a 1.5-fold (1.2-fold in the elderly) higher dose of oxcarbazepine. Deinduction will occur with the removal of carbamazepine (exceptions: CYP3A4/3A5 and UDP-glucuronyl transferase substrates). As a result, the metabolism of oxcarbazepine (and other agents) will slow over a period of several weeks, necessitating dose reduction in some cases.⁴³

TOPIRAMATE

Table III summarizes the results of case reports, case series, and controlled clinical trials of topiramate in neuropathic pain.^{49–56} The pharmacokinetic parameters of topiramate are summarized in Table II.

Pharmacokinetics

First evaluated as an oral hypoglycemic agent, topiramate is a sulfamate-substituted monosaccharide derived from D-fructose.¹⁷ Food has no clinically significant effect on its oral bioavailability. Despite its low-capacity, saturable binding to the carbonic anhydrase of red blood cells (RBCs), topiramate exhibits linear pharmacokinetics. Topiramate is principally eliminated by the renal route, with 55% to 66% of a dose eliminated as parent drug. Although metabolism, which is accomplished via oxidation and glucuronidation, is usually of minor importance in overall elimination of the drug, it becomes more important in patients receiving inducers of hepatic enzymes.

The findings of studies in healthy volunteers suggest that the pharmacokinetics of topiramate are not altered by advancing age.⁵⁷ However, in patients with epilepsy, a negative correlation has been found between the CL/F of topiramate and increasing age.⁵⁸ This may be explained, at least in part, by the effect of age-related reductions in renal function. In studies in patients with varying degrees of renal impairment, moderate (CrCl, 30–69 mL/min) and severe (CrCl, < 30 mL/min) renal impairment reduced the mean CL/F by 42% and 54%, respectively, compared with patients with mild renal impairment and normal renal function (CrCl > 70 mL/min). Hemodialytic clearance of topiramate was substantial (mean, 120 mL/min), suggesting that dose supplementation may be required at the end of the procedure.⁵⁷

Table III. Efficacy of topiramate (TOP) in the management of neuropathic pain.

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
49	Intercostal neuralgia	CR	1 (M)	60	25 mg HS, gradually increased to 75 mg HS, with addition of 25 and then 50 mg in morning. 6-mo follow-up.	75 mg HS produced 70%–80% pain relief and sleep throughout the night, but pain persisted during the day. Morning and HS dosing produced 80% pain relief throughout the day and night.
50	Variety of neuropathic pain syndromes	CS	14 (8 F, 6 M)	Range, 31–91	Weekly titration in increments of 25–50 mg to pain relief or MTD. Mean duration of therapy, 3.3 mo (range, 1–6 mo). Mean final daily dose, 271 mg (range, 100–800 mg).	Pain score was significantly reduced ($P < 0.001$) from a baseline mean of 8.8/10 (range, 5/10–10/10) to 3.1/10 (range, 0/10–8.5/10). First signs of relief were reported at a mean daily dose of 214 mg (range, 50–600 mg).
51	Refractory trigeminal neuralgia in MS patients	CS	5 (3 M, 2 F)	37 (range, 32–43)	25 mg BID initially, increased by 50 mg/d at weekly intervals based on response to a maximum of 200 mg BID. MTD continued for ≥ 6 mo.	4 Patients reported significant pain relief at 150 mg/d and complete relief at 200 mg/d; 1 patient required 300 mg/d for complete relief. Four (80%) patients discontinued concomitant analgesics. Response persisted for ≥ 6 mo. AE data NR.
52	Refractory trigeminal neuralgia in MS patients	CS	4 (3 F, 1 M)	57 (F), 35 (M), 58 (F), 39 (F)	All received 25 mg/d initially, increased by 25 mg/d q3d until pain relief or dosage reached 300 mg/d.	Patient 1 reached 300 mg/d and was pain free after 6 mo; patient 2 reached 150 mg/d and was pain free before 6 mo; patients 3 and 4 reached 200 mg/d and were pain free before 6 mo (patient 3 reported mild asthenia and dry mouth).
53	Various neuropathic pain syndromes	CS	4 (2 M, 2 F)	79 (M), 57 (F), 61 (M), 58 (F)	Patient 1 received 25 mg/d initially, which was gradually titrated to 200 mg/d (also received oxycodone 10 mg BID); dosage was subsequently tapered to 50 mg/d and titrated back to 100 mg/d (oxycodone was also increased to 20 mg BID). Patient 2 received 25 mg BID initially, which was increased to 50 mg BID after 2 mo. Patient 3 received 25 mg/d initially, with slow titration to 300 mg/d; dosage was subsequently increased to 400 mg/d and an SSRI started for increased pain. In patient 4, therapy was initiated and maintained at 25 mg/d.	Patient 1 perceived little pain relief and had clinically significant weight loss (28 lb) with TOP and oxycodone. After tapering to TOP 25 mg BID, pain increased markedly; at TOP 100 mg/d and oxycodone 40 mg/d, patient 1 felt that analgesia and weight loss were balanced. Patient 2 felt pain was greatly improved and was able to decrease opioid use from 8 to 2 tablets/d. After 2 mo, pain worsened and the dose was increased. Patient 2 still experienced pain, but to a much lesser degree. Patient 3 had 50% reduction in pain with 300 mg/d. Pain increased due to bereavement. At 400 mg/d plus an SSRI, patient 3 felt pain was much improved. Relief lasted ≥ 18 mo. After 4 mo, patient 4 experienced reduced allodynia/hyperalgesia. After 6 mo, the affected area was further reduced in size.

(continued)

Table III. (Continued)

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
53	Various neuropathic pain syndromes	R, PG	40 (NR)	NR	First 20 patients were randomized to receive 100 mg/d for 9 wk; 100 mg/d for 3 wk, increased to 200 mg/d for 6 wk; or 100 mg/d for 3 wk, increased to 200 mg/d for 3 wk and 300 mg/d for 3 wk. Second 20 patients received 25 mg/d initially, with titration over 9 wk to pain relief or MTD.	Thirteen (33%) patients completed 9 wk of therapy, of whom 9 (69%) reported improved pain control (CGI) and had a significant reduction (not defined) in pain score. Median SF-MPQ score decreased from 31 to 13 at a median dosage of 100 mg/d (range, 25–300 mg/d). 20 (50%) patients discontinued the study prematurely due to AEs, and the remainder were lost to follow-up.
54	Trigeminal neuralgia	R, DB, PC, CO	3 (2 F, 1 M)	40, 53, 66	25 mg/d initially (or a matching number of placebo capsules), titrated in increments of 25–50 mg/d twice weekly over the first 8 wk of each 12-wk phase to a maximum of 800 mg/d based on response.* Dose achieved at the end of wk 8 was maintained during wk 9–12. Phases were separated by a 2-wk washout period.	Based on data from last 2 wk of each phase, overall pain (on a 0–10 scale) decreased 31%, 42%, and 64% during TOP therapy in the 3 patients ($P = 0.04$); frequency of paroxysms decreased 10%–93% ($P = NS$), intensity of paroxysms decreased 3%–32% ($P = NS$), and duration of paroxysms decreased 77% in 1 patient and increased 88% and 290% in the other 2 ($P = NS$). AEs during active treatment included irritability and diarrhea (2 patients each) and fatigue/sedation, hyperactivity, nausea, abdominal cramps, light-headedness, and cognitive impairment (1 each).
54	Trigeminal neuralgia	R, DB, PC, CO	3 (2 F, 1 M)	40, 53, 66	Patients entered this confirmatory study if pain scores during the preliminary study favored TOP over placebo by ≥ 1 unit. Study included three 8-wk segments, in each of which patients received TOP for 4 wk and placebo for 4 wk in random order. TOP was given at the MTD from the preliminary study.	Only 2 patients completed all 3 crossovers (reasons for discontinuation NR). Considering the individual patients for all completed treatment periods, there was no significant effect on pain (overall or frequency, intensity, and duration of paroxysms). Considering the 3 patients together for all completed treatment periods, the results were the same. Pooling results of the preliminary and confirmatory studies and considering patients individually and together, the results were the same.

(continued)

Table III. (Continued)

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
55	Painful diabetic neuropathy	R, DB, PC, PG	27 (16 F; 11 M)	NR	Randomization to TOP or placebo (2:1), with titration of TOP to 200 mg BID or MTD over 9 wk, and maintenance of this dose for next 4 wk. All patients achieved MTD of 200 mg BID.	At final visit, patients receiving TOP (n = 18) had significantly less pain (<i>P</i> not provided) than those who received placebo (n = 9). Mean (SD) SF-MPQ and VAS scores were 11.1 (9.4) (<i>P</i> = 0.039) and 40.7 (28.6) (<i>P</i> = 0.007) for TOP vs 25.1 (11.7) and 70.4 (25.4) for placebo, respectively. Differences in the patient's global impression of change score were NS. Discontinuations due to AEs occurred in 5/18 (28%) patients receiving TOP and 1/9 (11%) patients receiving placebo (statistical analysis NR). The most common AEs due to TOP were asthenia, weight loss >10%, and confusion.
56	Painful diabetic neuropathy	R, DB, PC, PG	323 (NR)	NR	Randomization to TOP or placebo (2:1), with titration of TOP to 400 mg/d or MTD over 8 wk and maintenance of this dose for 4 wk. Mean (SD) daily dose, 161(78) mg.	Intent-to-treat population included 317 patients (208 TOP, 109 placebo); 192 completed the study (reasons for discontinuation NR). Mean baseline VAS scores (100-mm scale), 68.0 mm TOP, 69.1 mm placebo. At final visit, mean VAS scores were significantly different between groups (46.2 vs 54.0 mm, respectively; <i>P</i> = 0.038), as was the proportion of patients with ≥50% reduction in VAS scores (36% vs 21%; <i>P</i> = 0.005). Scores for worst pain over last week (<i>P</i> = 0.003), sleep disruption (<i>P</i> = 0.02), and patient's overall medication assessment (<i>P</i> = 0.002) significantly favored TOP. Mean weight change was significantly different between groups (−2.6 kg vs 0.2 kg; <i>P</i> < 0.001). Most common treatment-emergent AEs were diarrhea (11% and 4%), anorexia (11% and 1%), somnolence (10% and 4%), URTI (9% and 6%), and paresthesia (9% and 1%) (statistical analysis NR).

CR = case report; M = male; HS = at bedtime; CS = case series; F = female; MTD = maximum tolerated dose; MS = multiple sclerosis; AE = adverse event; NR = not reported; SSRI = selective serotonin reuptake inhibitor; R = randomized; PG = parallel-group; CGI = clinician's global impression; SF-MPQ = Short Form McGill Pain Questionnaire; DB = double-blind; PC = placebo-controlled; CO = crossover; VAS = visual analog scale; URTI = upper respiratory tract infection.

*Baseline analgesics could be continued during the study.

Drug Interactions

The enzyme inducers carbamazepine and phenytoin enhance the CL/F of topiramate by 40% to 50%. Primidone, phenobarbital, and oxcarbazepine also enhance topiramate CL/F. By an as-yet unknown mechanism, valproate reduces plasma concentrations of topiramate by a mean of 15%. Gabapentin and lamotrigine have no effect on topiramate CL/F. Topiramate reduces the CL/F of phenytoin by up to 25% in selected patients. This effect, which is the result of inhibition of the CYP2C19 isozyme, is inconsistent, occurring principally in patients at or near the saturation point of phenytoin metabolism. Topiramate reduces plasma concentrations of ethinyl estradiol by a mean of 30% (possibly mediated by induction of the CYP3A4 isozyme) and the C_{max} and AUC of digoxin by means of 16% and 12%, respectively (mediated by a nonrenal effect). Topiramate may enhance the hypoglycemic effect of metformin, although the mechanism by which this occurs is unknown.⁴⁰

Adverse Effects

The most common AEs reported in double-blind trials of topiramate in epilepsy^{17,19,41,45,46,57} were related to the CNS (ataxia, impaired concentration, confusion, dizziness, fatigue, digital and perioral paresthesia, somnolence, abnormal thinking, speech disturbances, language problems). The frequency and severity of these effects were increased at higher doses, with more rapid dose escalation, and when the drug was used as a component of combination therapy compared with its use as monotherapy.^{17,19,45,46,57} Topiramate has been reported to have negative effects on cognitive function in patients with epilepsy, with significant declines in fluency, attention/concentration, processing speed, language skills, perception, and working memory (but not retention).⁵⁹ Behavioral events such as aggression/agitation, emotional lability, euphoria, psychosis, and depression are seen rarely.⁴⁷ Nephrolithiasis (mainly calcium phosphate stones) is seen in ~1.5% of topiramate recipients; most stones are very small and are passed spontaneously. The development of nephrolithiasis is probably mediated by changes in urine pH due to carbonic anhydrase inhibition.

Two non-CNS AEs of topiramate are of particular interest. First, the drug may cause acute myopia and secondary angle-closure glaucoma, presumably mediated by carbonic anhydrase inhibition. These events almost always occur in the first month of therapy, are manifested by severe bilateral ocular pain and hyperemia, and usually remit within 24 hours of drug withdrawal.⁴⁵ Second, most topiramate recipients experience weight

loss, which becomes apparent within the first 3 months of therapy and peaks by 12 to 18 months. This weight loss appears to be dose related, with a 2% loss in body weight at dosages <200 mg/d and a 7% loss at dosages >1000 mg/d. Anorexia is a major contributor to this effect, at least initially. Obese patients experience greater weight loss than do nonobese patients. Beneficial effects on plasma glucose and lipid levels have been reported along with this weight loss.^{45,60}

As both agents have similar biochemical effects (particularly with respect to nephrolithiasis and weight loss), there may be a risk of additive toxicity with the combination of topiramate and zonisamide. However, the extent of this risk is unclear at present.³⁹

Dosing

Topiramate is available as 25-, 100-, and 200-mg oral tablets and 15- and 25-mg sprinkle capsules. Based on data from trials in epilepsy,^{17,19,41,45,46,57} the recommended starting dosage of topiramate in adults is 25 to 50 mg/d, followed by titration in 25- to 50-mg/d increments every 1 to 2 weeks, based on response, to a usual maintenance dosage of 200 to 400 mg/d (maximum, 600 mg/d). Doses are given twice daily. The sprinkle capsules may be swallowed whole, or the contents can be sprinkled on a small amount of soft food and swallowed without chewing. In patients with a CrCl <70 mL/min, the initial dose should be halved, followed by dose titration at a longer interval than usual (the longer $t_{1/2}$ prolongs time to steady state). There are no specific recommendations for dose supplementation after dialysis.^{17,57}

ZONISAMIDE

Table IV summarizes the results of case series concerning the use of zonisamide for neuropathic pain.⁶¹⁻⁶³ The pharmacokinetic parameters of zonisamide are summarized in Table II.

Pharmacokinetics

Zonisamide is 1,2-benzisoxazole-3-methanesulfonamide. Use of this agent is contraindicated in patients with sulfonamide allergies. Such use has resulted in several deaths secondary to complications of severe rash (including toxic epidermal necrolysis and Stevens-Johnson syndrome), leukopenia, and aplastic anemia.⁴¹

Food has no clinically significant effect on the oral bioavailability of zonisamide. The pharmacokinetics of this agent are nonlinear (ie, C_{max} and AUC do not increase in proportion to increasing dose). Zonisamide's

Table IV. Efficacy of zonisamide in the management of neuropathic pain.

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
61	Various neuropathic pain syndromes (eg, PDN, PN, RSD)	CS	35 (19 M, 16 F)	Mean, 52 (range, 25–88)	8-wk dose-titration period, followed by 2-wk maintenance period. Regimens NR.	17 (49%) patients completed study, 18 (51%) discontinued (1 for nonefficacy, 10 due to AEs, 4 for nonadherence, 3 for other reasons). Mean daily pain scores (10-point scale) decreased from 6.82 to 6.72. Slight improvements in mean scores on several WBPI categories. At end of therapy, pain relief scores indicated 3 patients felt worse, 21 had no change, 7 were improved/much improved, and 1 had complete pain relief. Mean neuropathic pain scores increased (worsened) from 49.71 to 51.10 at wk 8, then decreased (improved) to 49.41 at wk 10. Mean investigator's global assessment scores showed almost no change. AEs included abnormal thinking, asthenia, dizziness, nausea, headache, somnolence, dyspepsia, constipation, and paresthesia.
62	Various refractory neuropathic pain syndromes	CS	50 (NR)	NR	100 mg/d every 4th night for 4 doses, followed by 100 mg/d every 3rd night for 4–5 doses, 100 mg/d every other night for 5–6 doses, and 100 mg/d HS. Further dosage changes as needed q2wk. Final regimens and duration of therapy NR.	Twenty-six (65%) of 40 patients reaching the maintenance phase (100 mg/d) had improved pain scores; 18 were able to taper or discontinue previous AED therapy while taking zonisamide. Ten (20%) patients were still in the titration phase at the time of publication. Premature discontinuations due to AEs (drowsiness) occurred in 2 (4%) patients; 4 (8%) were lost to follow-up.
63	Various neuropathic pain syndromes	CS	132 (NR)	NR	Regimens and duration of therapy NR.	100 (76%) patients reported at least moderate improvement in pain; remainder reported minimal or no improvement. Of 105 patients who also wanted to lose weight, 76 (72%) achieved ≥70% of weight loss goal, and degree of weight loss was independent of the degree of pain relief; 100% of patients who had no pain relief (~32) achieved ≥80% of weight loss goal, reinforcing the independence of weight loss and pain relief. In total study population, mean weight loss was 25 lb and maximum was 100 lb.

PDN = painful diabetic neuropathy; PN = postherpetic neuralgia; RSD = reflex sympathetic dystrophy; CS = case series; M = male; F = female; NR = not reported; AEs = adverse events; WBPI = Wisconsin Brief Pain Inventory; AED = antiepileptic drug.

nonlinear pharmacokinetics are secondary to the extensive and saturable binding of zonisamide to the carbonic anhydrase of RBCs (RBC/plasma concentration ratio, ~8:1).

Although zonisamide's $t_{1/2}$ is sufficiently long to allow once-daily dosing, twice-daily dosing is recommended to reduce the percentage of fluctuation around the average steady-state plasma concentration (from 27% with once-daily dosing to 14% with twice-daily dosing). Zonisamide is eliminated by both hepatic metabolism and renal and fecal excretion. Its metabolism involves acetylation, reduction, and glucuronidation. The reduction reaction by which zonisamide is converted to 2-(sulfamoylacyl)-phenol (SMAP) is mediated by the CYP3A isozyme. Thirty-five percent of the dose appears in urine as parent drug, 15% as N-acetylzonisamide, and 50% as SMAP glucuronide.⁶⁴

The pharmacokinetics of zonisamide are not significantly altered by advancing age. No data are available regarding the effect of hepatic impairment on zonisamide's pharmacokinetics. Renal drug clearance decreases with decreasing CrCl: when CrCl is <20 mL/min, the mean AUC of zonisamide is increased 35%.⁶⁴

Drug Interactions

Concurrent use of hepatic enzyme inducers such as phenobarbital, carbamazepine, and phenytoin enhance the CL/F of zonisamide by 30% to 50%. In contrast, valproate and lamotrigine may increase plasma concentrations of zonisamide. When combined with phenytoin, zonisamide produces a modest increase in plasma concentrations of phenytoin (mean, 16%), probably via a weak inhibitory effect on the CYP2C19 isozyme. Assessments of the effect of zonisamide on the pharmacokinetics of carbamazepine have produced variable results, although most data support metabolic inhibition (ie, plasma concentrations of carbamazepine increase and those of its epoxide metabolite decrease).⁴⁰

Adverse Effects

The most common AEs of zonisamide reported in double-blind trials in epilepsy were somnolence, ataxia, anorexia, confusion, abnormal thinking, nervousness, fatigue, and dizziness.^{18,41,64} Paresthesia, seen with other carbonic anhydrase inhibitors, is infrequently seen with zonisamide. Behavioral events such as psychosis, mania, depression, agitation, and irritability occur rarely.⁴⁷ Although less problematic than with topiramate, clinically significant weight loss may occur with zonisamide.⁴⁵

The occurrence of nephrolithiasis in early clinical trials led to temporary suspension of US/European trials

of zonisamide in the 1980s. Although this occurred rarely in Japan (incidence, <0.2%), 2% to 4% of US/European patients developed stones of varied composition (urate, calcium oxalate, calcium phosphate). The majority of these stones were small and required no treatment. Alterations in urine pH due to carbonic anhydrase inhibition is the probable mechanism of this effect. Adequate hydration is necessary for safe use of this agent.¹⁸

Again, the potential for additive toxicity when zonisamide and topiramate are used together remains unresolved.⁴¹

Dosing

Zonisamide is available as a 100-mg oral capsule. Based on data from trials in epilepsy,^{18,41,64} the recommended starting dosage of zonisamide in adults is 100 to 200 mg/d, followed by dose titration every 2 weeks, based on response, to a usual maintenance dosage of 400 to 600 mg/d. Doses are given twice daily. No specific dosing recommendations are available for patients with hepatic or renal impairment.⁶⁴

LEVETIRACETAM

Table V summarizes the results of case series concerning the use of levetiracetam for neuropathic pain.⁶⁵⁻⁶⁹ The pharmacokinetic parameters of levetiracetam are summarized in Table II.

Pharmacokinetics

Levetiracetam is the *S*-enantiomer of a racemic (*R,S*) pyrrolidine acetamide.⁴⁰ Food has no clinically significant effect on its oral bioavailability. The pharmacokinetics of levetiracetam are linear. Drug elimination is by both metabolism and renal excretion. Metabolism occurs principally through hydrolysis of the acetamide group—a non-CYP-dependent reaction—to the main metabolite, UCB-LO57 (accounting for 24% of the dose). Two other minor metabolites are produced, together accounting for <3% of the dose. Renal elimination of parent compound and metabolites accounts for a respective 66% and 27% of the dose.

The mean CL/F is reduced by 38% and the $t_{1/2}$ is prolonged by 2.5 hours in elderly volunteers (age 61–88 years) compared with young volunteers (age not stated). These differences can be explained by age-related reductions in CrCl. The pharmacokinetics of levetiracetam are not significantly altered in patients with mild or moderate hepatic impairment (Child-Pugh class A or B), but the mean CL/F is reduced by 50% in those with severe

Table V. Efficacy of levetiracetam in the management of neuropathic pain.

Ref.	Pain Condition	Study Design	No. of Pts. (Sex)	Age, y	Regimen	Results
65	Refractory neuropathic pain in MS patients	CS	20 (NR)	NR	Titration to 500–4500 mg/d (titration scheme and duration of therapy NR).	Twelve (60%) patients had moderate to marked improvement in pain symptoms, 3 (15%) mild improvement, and 5 (25%) no improvement. 1 Patient discontinued therapy at 500 mg/d due to fatigue and disorientation. Other possible AEs included weakness, urinary retention, worsening spasticity, and numbness (incidences NR). Two (17%) of the 12 patients with moderate to marked improvement were able to discontinue all pain medications after 4–8 mo of treatment.
66	Neoplastic plexopathies	CS	6 (NR)	NR	Titration over ≤14 d. Maximum daily dose, 1000–3000 mg. Concurrent tapering of opioids attempted in all patients. Duration of therapy NR.	VAS pain score (10-cm scale) decreased from 8–9 cm at baseline to 0–3 cm within 3–14 d. Opioid use decreased by >50%. No AEs reported.
67	Various neuropathic pain syndromes	CS	15 (9 F, 6 M)	Range, 30s–90s (11 aged ≥60 y)	Titration scheme NR. Final daily dose, 1000–2000 mg (mean, 1400 mg). Mean duration of treatment, 3 mo.	Ten (67%) patients found drug significantly effective or very effective in reducing pain. AEs occurred in 2 (13%) patients: dry eyes leading to discontinuation in 1 and dizziness in the other.
68	Various neuropathic pain syndromes	CS	35 (NR)	NR	Titration scheme NR. Duration of therapy, 30–90 d. Final daily dose, 250–1500 mg (mean, 750 mg).	Pain was improved in 20 (57%) patients, was unchanged in 11 (31%), and worsened in 1 (3%). 3 (9%) patients discontinued therapy due to AEs. Mean reduction in pain score (10-point scale) from baseline, 2.25 points (range, 0–7).
69	Various neuropathic pain syndromes	CS	25 (NR)	NR	Titration scheme and duration of therapy NR. Final daily dose, 1000–3000 mg (mean, 1840 mg).	On a 4-step pain scale (none, mild, moderate, severe), 12% improved one half step, 48% improved 1 step, and 24% improved 2 or 3 steps. Six (24%) patients discontinued therapy due to AEs (mainly drowsiness, sedation, ataxia). No data on AEs in remaining patients.

MS = multiple sclerosis; CS = case series; NR = not reported; AEs = adverse events; VAS = visual analog scale; F = female; M = male.

hepatic impairment (Child-Pugh class C), with the majority of the reduction due to reduced renal clearance. The CL/F of levetiracetam is correlated with CrCl: CL/F is reduced by respective means of 40%, 50%, 60%, and 70% in patients with mild (CrCl, 51–80 mL/min), moderate (CrCl, 30–50 mL/min), and severe renal impairment (CrCl, <30 mL/min), and end-stage (anuric) renal disease. A 4-hour hemodialysis session removes ~50% of the levetiracetam body pool.^{70,71}

Drug Interactions

No clinically significant drug interactions with levetiracetam have been identified to date.⁴⁰

Adverse Effects

Based on double-blind trials in epilepsy,^{19,41,71} the most frequent AEs with levetiracetam include dizziness, headache, fatigue, somnolence, and asthenia. Behavioral effects such as psychosis, depression, emotional lability, hostility, and nervousness are rare, although their risk is increased in the developmentally disabled and those with a history of psychiatric disorders.^{19,47}

Dosing

Levetiracetam is available as 250-, 500-, and 750-mg oral tablets. Based on data from the epilepsy trials,^{19,41,71} the recommended starting dosage in adults is 500 to 1000 mg/d, followed by titration every 2 weeks, based on response, to a usual maintenance dosage of 1000 to 3000 mg/d. The drug is given twice daily. Assuming a target dosage of 500 to 1500 mg BID in patients with normal CrCl (>80 mL/min), the respective target dosages in mild, moderate, severe, and end-stage renal disease (as defined earlier in this section) are 500 to 1000 mg BID, 250 to 750 mg BID, 250 to 500 mg BID, and 500 to 1000 mg once daily, with a 250- to 500-mg supplemental dose after each hemodialysis session.^{19,71}

ASPECTS OF GERIATRIC USE OF THE NEWER AEDS

All 4 newer AEDs have the potential to enhance the CNS AEs of concomitant psychotherapeutic drugs (eg, pharmacodynamic interactions with opioids, antidepressants, neuroleptics). Although not as problematic as older AEDs, these agents (with the exception of levetiracetam) can interact pharmacokinetically with other drugs. Most studies of drug interactions with these agents have concentrated on interactions with other AEDs and not on interactions with other drugs commonly used in older

individuals. Knowing which drugs are metabolized by which CYP isozymes, as well as their relative potency of enzyme induction or inhibition, can help the clinician anticipate clinically significant interactions.

In addition to CNS AEs, other AEs that can occur soon after initiation of therapy may be problematic in older patients. These include hyponatremia with oxcarbazepine, nephrolithiasis with topiramate and zonisamide, acute myopia with secondary angle-closure glaucoma with topiramate, and weight loss with topiramate and zonisamide. Older individuals frequently have diseases or take medications that can reduce serum sodium levels. The use of oxcarbazepine in such patients may result in symptomatic hyponatremia. The challenge of ensuring adequate hydration in frail elderly individuals (particularly residents of long-term care facilities) can make the use of zonisamide problematic in this population. Difficulties of ensuring adequate caloric intake and maintaining body weight can make the use of topiramate equally challenging in underweight elderly patients.

CONCLUSIONS

Preliminary data suggest that the newer AEDs oxcarbazepine, topiramate, zonisamide, and levetiracetam may be useful in the treatment of a variety of neuropathic pain syndromes, although full reports of controlled trials are required. These agents are associated with specific AEs not commonly monitored by clinicians. Clinicians intending to use these drugs should familiarize themselves with their clinical pharmacology. Of the 4 agents, levetiracetam appears to be the easiest to use (ie, no need for dose adjustment in organ dysfunction, no need for laboratory monitoring) and best tolerated, and has not been associated with the unique toxicities reported for oxcarbazepine, topiramate, and zonisamide. Determination of the role of these agents in the therapeutic armamentarium against pain will require further research and experience. In the interim, these 4 agents should be used to treat neuropathic pain in the elderly only when carbamazepine, gabapentin, or lamotrigine cannot be used or when the response to the aforementioned agents is suboptimal.

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